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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/865,281	KOHLER, HEINZ	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-35 are pending.

2. Claims 1-20 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. The following new grounds of rejections are necessitated by the amendment filed 11/22/04.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 21-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a fusion protein comprising an anti-idiotypic anti-CEA antibody fused to a peptide consisting of SEQ ID NO: 1 which derived from the C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhances the immunogenicity of the claimed anti-idiotypic antibody, **does not** reasonably provide enablement for any fusion protein as set forth in claims 21-35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only anti-idiotypic antibody 3H1 that induces anti-CEA antibody fused to a peptide consisting of SEQ ID NO: 1. The peptide of SEQ ID NO: 1 is derived from the C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhances

the immunogenicity of the anti-idiotypic antibody (See page 15-16). The anti-idiotypic antibody can be used as CEA antigen for making anti-CEA antibody.

The specification does not teach how to make and use any antigen-binding fusion protein comprising any antibody, any antibody such as antibody that binds to any cellular receptor on normal cell or tumor cell, fused to any peptide, any peptide such as peptide with homophilic activity, peptide with immunostimulatory activity, and peptide has inverse hydrophathicity within the length of the undisclosed peptide, any peptide having any membrane transport activity because of the following reasons. A peptide in the claimed fusion protein with homophilic activity, immunostimulatory activity and/or transport activity without the amino acid sequence has no structure. There is insufficient guidance as to the structure of the peptide without the amino acid sequence, let alone the length of the peptide wherein the peptide has inverse hydropathicity, has immuno-stimulatory activity, membrane transport activity or homophilic binding activity. Without knowing the amino acid sequence (the length) of the peptide in the fusion protein, one skilled in the art cannot make any "inverse hydrophathicity within the length of said peptide". Further, there is in sufficient guidance as to the binding specificity of the antibody in the antigen-binding fusion protein. There is insufficient guidance as to which cellular receptor on normal cell and which cellular receptor on tumor cell that the claimed antigen binding fusion protein binds. Since the structure (amino acid sequence) of the antigen-binding fusion protein is not enabled, it follows that the nucleic acid encoding the undisclosed antibody and peptide, as a fusion product is not enabled.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities.

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific

conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular).

With regard to "antibody comprises a light chain *or* heavy chain immunoglobulin" as recited in claims 22, 27, 29, 30, 33 and 34, there is a lack of guidance and working example demonstrating that antibody comprises either light chain or heavy chain is capable of binding to any antigen. The state of the antibody art as exemplified by Harlow et al is such that antibody binding to antigen requires both the variable domains of heavy *and* light chains to form an antigen binding site (see page 8-9, Figure, in particular).

Given the unlimited number of undisclosed antigen binding fusion protein comprising undisclosed antibody and undisclosed peptide, there is insufficient working example demonstrating that any peptide when fused to any antibody will resulted in immunostimulatory activity, membrane transport activity, and/or homophilic activity. Given the unlimited number of undisclosed antigen binding fusion protein, it is unpredictable which undisclosed antigen binding fusion protein would be useful for which purpose.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 11/22/04 have been fully considered but are not found persuasive.

Applicants' position is that the present specification provides highly detailed guidance in teaching those skilled in the art how to make and use the invention. The skilled artisan following the teachings in the specification could practice the claimed invention with routine, if any,

experimentation. The Examiner's attention is respectfully directed to, for example, the specification at page 4, lines 7 to 25, pages 10 to 14, and the Examples, wherein methods for creating a fusion protein under the invention are disclosed. Applicant submits that these examples clearly teach those skilled in the art how to practice the invention as claimed and, as such, that the application is fully enabled. Applicant respectfully points out that the invention as presently claimed is not limited to a fusion protein with any particular peptide (or amino acid sequence). Rather, the fusion proteins in various embodiments of the invention include a peptide possessing homophilic, immuno-stimulatory and/or membrane transport activities, where the peptide does not interfere with antigen binding. The skilled artisan can readily determine whether said peptide comprises one or more of the aforementioned activities. In a similar fashion, the invention as presently claimed is not meant to be limited to any particular antibody binding specificities, immunoglobulin heavy or light chains or cellular receptor on a normal or a tumor cell. Rather, the invention as presently claimed can be used in a myriad of combinations, the details of which are known to those skilled in the art. The invention as presently claimed features fusion protein comprising (1) an antibody and (2) a peptide with homophilic, immuno-stimulatory and/or membrane transport activities, where the peptide does not interfere with antigen binding, regardless of the conformation.

In response, the specification discloses only anti-idiotypic antibody 3H1 that induces anti-CEA antibody fused to a peptide consisting of SEQ ID NO: 1. The peptide of SEQ ID NO: 1 is derived from the C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhances the immunogenicity of the anti-idiotypic antibody (See page 15-16). The anti-idiotypic antibody can be used as CEA antigen for making anti-CEA antibody.

The specification does not teach how to make and use any antigen-binding fusion protein comprising any antibody, any antibody such as antibody that binds to any cellular receptor on normal cell or tumor cell, fused to any peptide, any peptide such as peptide with homophilic activity, peptide with immunostimulatory activity, and peptide has inverse hydrophathicity within the length of the undisclosed peptide, any peptide having any membrane transport activity because of the following reasons. A peptide in the claimed fusion protein with homophilic activity, immunostimulatory activity and/or transport activity without the amino acid sequence has no structure. There is insufficient guidance as to the structure of the peptide without the amino acid sequence, let alone the length of the peptide wherein the peptide has inverse hydropathicity, has immuno-stimulatory activity, membrane transport activity or homophilic

binding activity. Without knowing the amino acid sequence (the length) of the peptide in the fusion protein, one skilled in the art cannot make any "inverse hydrophathicity within the length of said peptide". Further, there is in sufficient guidance as to the binding specificity of the antibody in the antigen-binding fusion protein. There is insufficient guidance as to which cellular receptor on normal cell and which cellular receptor on tumor cell that the claimed antigen binding fusion protein binds. Since the structure (amino acid sequence) of the antigen-binding fusion protein is not enabled, it follows that the nucleic acid encoding the undisclosed antibody and peptide, as a fusion product is not enabled. Without the structure of the antigen-binding fusion protein, in essence, applicant asks one skilled in the art to go figure themselves what the claimed antigen-binding fusion protein look like.

6. Claims 21-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of all antigen-binding fusion protein comprising any antibody, any antibody such as any antibody that binds to any cellular receptor on normal cell, any antibody that binds to any cellular receptor on tumor cell, fused to any peptide, any peptide such as peptide with homophilic activity, peptide with immunostimulatory activity, and peptide has inverse hydrophathicity within the length of the undisclosed peptide, any peptide having any membrane transport activity without the amino acid sequence.

The specification discloses only anti-idiotypic antibody 3H1 that induces anti-CEA antibody fused to a peptide consisting of SEQ ID NO: 1 which derived from the C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhance the immunogenicity of the anti-idiotypic antibody that was used as CEA antigen (See page 15-16).

With the exception of the specific antigen-binding fusion protein mentioned above, there is insufficient written description about the structure associated with function of all antigen-binding fusion protein without the amino acid sequence. There is insufficient written description about the structure of the peptide associated with which function in the claimed antigen-binding fusion protein without the amino acid sequence, let alone which undisclosed peptide has immuno-stimulatory activity, which undisclosed peptide has membrane transport activity and which

undisclosed peptide has homophilic activity when fused to all antibody. With regard to the antibody in the claimed fusion protein, there is inadequate written description about the binding specificity of the antibody in the antigen-binding fusion protein. Given the unlimited number of antigen-binding fusion protein, there is insufficient written description about the cellular receptor on normal cell and the cellular receptor on tumor cell that the claimed antigen-binding fusion protein binds. Since the structure or amino acid sequence of the antigen-binding fusion protein is not adequately described, it follows that the nucleic acid encoding said fusion protein is not adequately described.

Finally, given the lack of an additional species of antigen-binding fusion protein, peptide, antibody that binds to any cellular receptor on normal or tumor cell, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 11/22/04 have been fully considered but are not found persuasive.

Applicants' position is that the application as filed fully describes and exemplifies the claimed invention. As such, there can be no doubt that Applicant had possession of the claimed invention at the time the application was filed. The invention as presently claimed features fusion proteins which, in various embodiments of the invention, comprise an antibody and a peptide comprising homophilic, immuno-stimulatory and/or membrane transport activity. Description of each of these embodiments of the invention are provided in the specification as filed (including the references incorporated thereinto).

In response, The specification discloses only anti-idiotypic antibody 3H1 that induces anti-CEA antibody fused to a peptide consisting of SEQ ID NO: 1 which derived from the C3d region 1217-1232 that binds to the CR2 receptor on B cells and enhance the immunogenicity of the anti-idiotypic antibody that was used as CEA antigen (See page 15-16).

With the exception of the specific antigen-binding fusion protein mentioned above, there is insufficient written description about the structure associated with function of all antigen-

binding fusion protein without the amino acid sequence. There is insufficient written description about the structure of the peptide associated with which function in the claimed antigen-binding fusion protein without the amino acid sequence, let alone which undisclosed peptide has immuno-stimulatory activity, which undisclosed peptide has membrane transport activity and which undisclosed peptide has homophilic activity when fused to all antibody. With regard to the antibody in the claimed fusion protein, there is inadequate written description about the binding specificity of the antibody in the antigen-binding fusion protein. Given the unlimited number of antigen-binding fusion protein, there is insufficient written description about the cellular receptor on normal cell and the cellular receptor on tumor cell that the claimed antigen-binding fusion protein binds. Since the structure or amino acid sequence of the antigen-binding fusion protein is not adequately described, it follows that the nucleic acid encoding said fusion protein is not adequately described.

Finally, given the lack of an additional species of antigen-binding fusion protein, peptide, antibody that binds to any cellular receptor on normal or tumor cell, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 28 is rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,314,995 (of record, May 1994, PTO 892).

The '995 patent teaches a fusion protein made up of an antibody such as anti-tumor antigen L6 antibody and peptides such as IL-2, and IL6 having a immunostimulatory activity such as lymphocyte proliferation (See column 2, line 38-42, summary of the invention, in particular). The reference IL-2 peptide is connected to a site such as the Fc region of the reference antibody that does not interfere the reference antibody from binding to tumor cells. The reference fusion protein is created by a process comprising the steps of creating a fusion

product comprising a nucleic acid sequence encoding the reference antibody and a nucleic acid sequence encoding the reference peptide (See Fig 6A-10, column 3, Construction of recombinant genes encoding antibody fusion proteins, in particular). The '995 patent teaches that the reference antibody is the variable region of the light and heavy chain of the anti-tumor antigen monoclonal antibody (See column 2, line 52, lines 55, in particular). The reference antibody based fusion proteins are useful as a method of delivering biologically active ligand molecules to the target cells or tissues and offers the advantage of decreasing systemic exposure to lymphokines and minimizing toxic effects (See column 8, lines 21-26, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 11/22/04 have been fully considered but are not found persuasive.

Applicants' position is that U.S. Patent 5,314,955 is not of record in this application. Applicant is thus of the belief that the Examiner is referring to U.S. Patent 5,314, 995, which is of record. Applicant's remarks that follow are based upon this belief. The fusion construct described in the cited patent is not shown to have an immuno-stimulatory activity.

In response, the Examiner apologizes for the inadvertent typographical error in this rejection. Applicant is correct to assume that the rejection is based on the 5,314, 995 patent as cited on the PTO 892. In contrast to applicant's assertion that the fusion protein of the '995 patent does not have an immuno-stimulatory activity, the '995 patent teaches a fusion protein made up of an antibody such as anti-tumor antigen L6 antibody and peptides such as IL-2, and IL6 having a immunostimulatory activity such as lymphocyte proliferation (See column 2, line 38-42, summary of the invention, in particular). The reference IL-2 is used to stimulate T cell proliferation and treating tumor.

9. Claims 28 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,698,679 (Dec 1997, PTO 1449).

The '679 patent teaches an antigen-binding fusion protein comprising an antibody that binds specifically to a cellular receptor such as CD40 on normal cell such as APC cells and B cells fused to an immunogenic peptide such as ovalbumin 326-337 (See entire document, column 25, example 2, column 8, lines 43-50, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 11/22/04 have been fully considered but are not found persuasive.

Applicants' position is that U.S. Patent 5,698,679, neither teaches nor suggests such a fusion protein. Applicant notes that in paragraph 16 of the Official Action, the Examiner indicates that the application currently names joint inventors. However, the application currently names a single inventor. Applicant respectfully requests acknowledgement in the next Official Action that Dr. Heinz Kohler is the sole listed inventor of record in the U.S. Patent and Trademark Office for the present application.

In contrast to applicant's assertion that the '679 patent does not teach a fusion protein, The '679 patent teaches an antigen-binding fusion protein comprising an antibody that binds specifically to a cellular receptor such as CD40 on normal cell such as APC cells and B cells fused to an immunogenic peptide such as ovalbumin 326-337 (See entire document, column 25, example 2, column 8, lines 43-50, in particular). Thus, the reference teachings anticipate the claimed invention.

In response to applicant's request in acknowledgement that Dr. Heinz Kohler is the sole listed inventor of record, Heinz Kohler is the sole inventor of record. Paragraph 16 in the previous Office Action does not apply in instant case.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 21, and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,314,995 (of record, May 1994, PTO 892) or US Pat No 5,698,679 (Dec 1997, PTO 1449) each in view of Kang *et al* (Science 240: 1034-36, 1988; PTO 1449), and Yan et al (J Immunology 157: 1582-88, 1996; PTO 892).

The teachings of the '955 patent and the '679 patent have been discussed supra.

The claimed invention in claims 21 and 23 differs from the teachings of the references only in that the antigen binding fusion protein wherein the peptide has homophilic activity.

The invention in claim 26 differs from the teachings of the references only in that the antigen binding fusion protein wherein the peptide that has inverse hydrophathicity within the length of said peptide.

Kang et al teach various peptides derived from Variable Heavy and Variable Light chain of antibody T-15-M603 wherein the reference peptide has homophilic activity or self binding activity and is proximal to the antigen binding of the antibody T15-M603 (see page 240, col. 1, first full paragraph, in particular). The reference peptides have inverse hydrophathicity within the length of said peptide (see page 1035, Table 3, in particular). Kang et al teach self-binding site is functionally related to antigen binding site (see page 1036, col. 1, in particular).

Yan et al teach the homophilic binding region of an antibody such as mAb directed against GD3 ganglioside appears to require for high avidity binding to the cell surface antigen GD3 (see page 1582, col. 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the immunostimulatory peptide IL2 or IL6 in the fusion protein as taught by the '995 patent or the immunogenic ovalbumin 326-337 peptide in the antigen binding fusion protein as taught by the '679 patent for the peptide that has homophilic activity and inverse hydrophathicity within the length of said peptide as taught by Kang et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to combine the references because Yan et al teach that homophilic binding region of an antibody appears to require for high avidity binding to the cell surface antigen GD3 (see page 1582, col. 2, in particular). Kang et al teach self-binding site is functionally related to antigen binding site (see page 1036, col. 1, in particular).

12. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rojas *et al* (J Biol Chem 271(44): 27456-61, 1996; PTO 892) in view of Bhattacharya-Chatterjee *et al* (J Immunology 145: 2758-2785, 1990; PTO 1449) or WO 96/20219 publication (July 1996, PTO 892).

Rojas *et al* teach a fusion protein comprising a cell membrane translocating sequence AAVALLPAVLLALLAP fused to phosphopeptide (See Figure 1, page 27457, column 1, in particular). Rojas *et al* teach by introducing functionally distinct domains such as the reference cell membrane translocating peptide in the fusion protein, this peptide would function as a carrier

and would have been expected to deliver various cargo into the cell, which is useful for designing therapeutic molecular drugs for tumors related to oncogenes (See page 27461, column 1, in particular).

The invention in claim 32 differs from the teachings of the reference only in that the fusion protein comprising an antibody instead of phosphopeptide fused to a peptide having a membrane transport activity and does not interferes with antigen binding.

Bhattacharya-Chatterjee *et al* teach an anti-idiotype antibody such as 3H1 that elicits the production of anti-CEA antibody that binds specifically to carcinoembryonic antigen (CEA) on normal and tumor cell in colon carcinoma (See abstract, Materials and Methods on page 2759, page 2760, column 2, 2nd paragraph, page 2761, column 1, 2nd paragraph, in particular). Bhattacharya-Chatterjee *et al* teach antibody 3H1 appears to functionally mimics CEA antigen and has the potential to be used as a network antigen for CEA to induce anti-tumor immunity in GI cancer patients (See page 2759, column 1, first paragraph, in particular).

The WO 96/20219 publication teaches various antibody such as anti-idiotype antibody 3H1 that elicits specific antibody response to CEA in various species such as mice, rabbits and monkeys and humans associated with advanced CEA associated disease (See abstract, in particular). The WO 96/20219 publication teaches a pharmaceutical composition comprising the reference antibody and a pharmaceutically acceptable excipient and/or adjuvant for eliciting immune response with advanced CEA associated disease (See claims 7-13 of WO 96/20219 publication). The WO 96/20219 publication teaches the reference antibody 3H1 can be used as a CEA antigen substitute to induce anti-tumor immunity in gastrointestinal cancer patients with advanced CEA associated disease because immunization with intact CEA molecule might trigger potentially harmful autoimmune reactions (See paragraph bridging pages 4 and 5, lines 1-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the phosphopeptide in the fusion protein as taught by Rojas *et al* for the antibody such as anti-CEA antibody of anti-idiotype antibody as taught by Bhattacharya-Chatterjee *et al* or the WO 96/20219 publication for an antigenic binding fusion protein made up of anti-idiotype antibody such as 3H1 fused to a peptide that has membrane translocating activity as taught by Rojas *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to combine the references because Rojas *et al* teach by introducing functionally distinct domains such as the reference cell membrane translocating peptide in the fusion protein, this peptide would function as a carrier and would have been expected to deliver various cargo into the cell such as tumors (See page 27461, column 1, in particular). Bhattacharya-Chatterjee *et al* teach an anti-idiotype antibody such as 3H1 elicits the production of anti-CEA antibody that binds specifically to carcinoembryonic antigen (CEA) on normal and tumor cell such as colon carcinoma. Bhattacharya-Chatterjee *et al* teach antibody 3H1 appears to functionally mimics CEA antigen and has the potential to be used as a network antigen for CEA to induce anti-tumor immunity in GI cancer patients (See page 2759, column 1, first paragraph, in particular). The WO 96/20219 publication teaches the reference antibody 3H1 can be used as antigen CEA substitute to induce anti-tumor immunity in gastrointestinal cancer patients with advanced CEA associated disease because immunization with intact CEA molecule might trigger potentially harmful autoimmune reactions (See paragraph bridging pages 4 and 5, lines 1-12, in particular).

13. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rojas *et al* (J Biol Chem 271(44): 27456-61, 1996; PTO 892) in view of Bhattacharya-Chatterjee *et al* (J Immunology 145: 2758-2785, 1990; PTO 1449) or WO 96/20219 publication (July 1996, PTO 892) as applied to claim 32 mentioned above and further in view of

The combined teachings of Rogas et al and Bhattacharya-Chatterjee *et al* or the WO 96/20219 publication have been discussed supra.

The invention in claim 35 differs from the teachings of the combined references only in that the antigen fusion protein wherein the antibody is specific for a cellular receptor on a normal cell or a tumor cell.

The '171 patent teaches antibody such as 3E8 that binds to a cellular receptor on tumor cell such as HER2 receptor (see entire document, col.3, line 64-64, Col. 19, Table 2, in particular). The reference antibody is useful for treating tumor (see col. 3, lines 64-65, Summary of invention, in particular).

Therefore, Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the anti-CEA antibody as taught by Bhattacharya-Chatterjee *et al* or WO 96/20219 publication in the antigen binding fusion protein comprising an antibody and a membrane transport peptide as taught by Rogas et al and Bhattacharya-Chatterjee

et al or the WO 96/20219 publication for the antibody that is specific for a cellular receptor on tumor cell as taught by the '171 patent and a peptide having membrane transport activity. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to substitute because the '171 patent teaches antibody to HER2 receptor on tumor cell is useful for treating cancer(see col. 3, lines 64-65, Summary of invention, in particular). Rojas *et al* teach the cell membrane translocating peptide in the fusion protein that function as a carrier would have been expected to deliver various cargo into the cell, which is useful for designing therapeutic molecular drugs for tumors related to oncogenes (See page 27461, column 1, in particular).

14. Claims 22, 27, 29-30 and 33-34 are free of prior art.

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone

are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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February 18, 2005

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